Specialty Conference

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Coronary Artery Spasm

Pathophysiology, Clinical Presentations, Diagnostic Approaches and Rational Treatment

DONALD C. HARRISON, MD:* In the past decade coronary artery spasm has been increasingly appreciated as a cause of angina pectoris. The recognition of this clinical syndrome has intensified the search for specific diagnostic techniques and a rational approach to therapy based on sound physiologic understanding of coronary vascular control mechanisms. Our purpose in this conference is (1) to present our current understanding of the pathophysiologic basis for coronary artery spasm, focusing on factors that control coronary artery contraction, (2) to discuss the varied clinical presentations of coronary artery spasm in patients with normal coronary arteries and in those with fixed obstructive disease and (3) to present a rational approach to treatment of these patients, emphasizing the use of the new drugs that block calcium channels in arterial smooth muscle cells.

Historical Background

In 1959 Prinzmetal and associates[1] reported findings on a small group of patients with "variant angina" who had transient ST segment elevation during episodes of chest pain. These patients were unique in that their angina usually occurred at rest or at night in a cyclic and recurrent manner. One of these patients died and was found to have severe occlusive coronary artery disease. The authors therefore postulated that variant angina was caused by spasm superimposed on areas of severe, fixed, occlusive coronary artery disease that caused the pronounced transmural ischemia and ST segment elevation. Previous writers as far back as Osler[2] had wondered about the possible contribution to angina pectoris of changes in the diameter of coronary arteries. In 1910 Osler defined angina pectoris as a disease associated with changes in the arterial wall that were "organic or functional." Other observers, such as Wilson and Johnston,[3] noted in 1941 that "attendant myocardial ischemia is due to a change in caliber of coronary arteries affected, rather than by an increase in work of the heart." Whereas it was initially believed that coronary artery spasm was a rare, variant form of angina, the advent of coronary arteriography in the late 1960's and the ability to do continuous hemodynamic monitoring in the 1970's provided a great deal of insight into the wide spectrum of patients who may have varying degrees of coronary artery spasm contributing to their anginal syndrome.

Coronary Vascular Smooth Muscle Physiology

ROBERT GINSBURG, MD:† The human epicardial coronary artery is classified histologically as a muscular artery. It varies from 1 to 4 mm in diameter and is composed of four distinct layers: intima, internal elastic lamina, media and adventitia. The intima consists only of endothelial cells and a basal lamina. The media, or middle layer of the vascular wall, is made up of smooth muscle cells and bundles of collagenous fibrils and is separated from the intima by a distinct fenestrated internal elastic lamina. Nerves, capillaries and connective tissue comprise the outermost layer,

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
ECG = electrocardiogram
PGs = prostaglandins
PGI_2 = prostacyclin
Tx = thromboxane

the adventitia (Figure 1). Electron microscopy of the coronary artery has revealed that the smooth muscle cells of the coronary artery are connected to one another by areas called nexus or tight junctions.[4] These are areas of cell membrane apposition. They allow the smooth muscle cells of the human epicardial coronary artery to communicate with one another, sharing both biochemical and electrical signals, and thus operating as a functional unit.

The smooth muscle cells of the human coronary artery depend on extracellular calcium (Ca^{2+}) for contraction and maintenance of tone. Although many factors can regulate coronary tone, such as myocardial oxygen demand, the state of the autonomic nervous system and the level of circulating vasoactive substances, all of these events are regulated through a final common pathway. This pathway involves calcium.

In the normal resting state there is a large calcium gradient across the cell membrane: 10^{-3}M Ca^{2+} on the outside cell and 10^{-7}M Ca^{2+} on the inside. When the smooth muscle cell is excited, channels or pores located in the cell membrane open and calcium rushes into the cytoplasm of the cell. The calcium then complexes with the protein calmodulin, activates myosin kinase and the result is contraction of the cell. This "trigger" calcium enters the cell and is involved in normal as well as abnormal contraction of the smooth muscle cell. Conversely, agents that block the entry of calcium into the cell at the level of the membrane will prevent contraction.

Potential Mechanisms of Coronary Artery Spasm

The exact cause of coronary artery spasm is as yet unknown though there is active ongoing re-

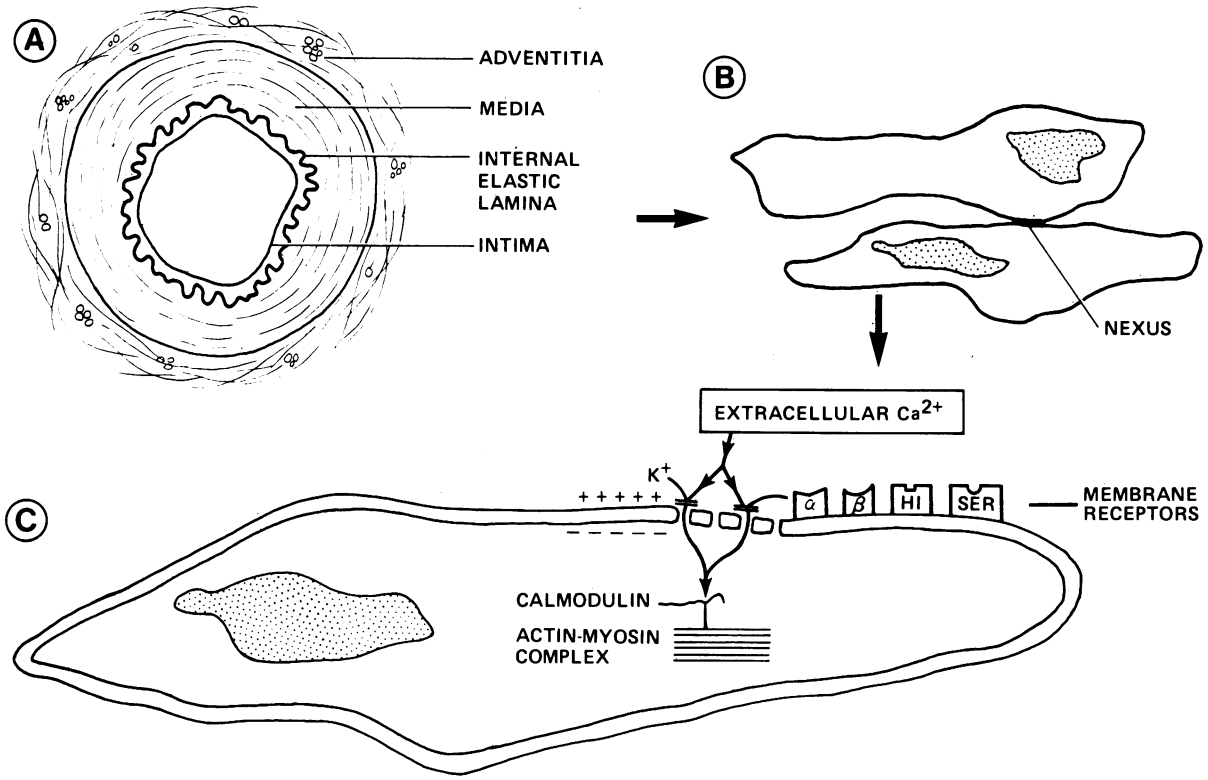

Figure 1.—A, Schematic cross-section of human epicardial coronary artery. (Reduced from magnification ×100.) **B,** Schematic of two smooth muscle cells showing nexus or gap junction—an area of cell membrane apposition. (Reduced from magnification ×4,000.) **C,** Schematic diagram of calcium (Ca^{2+}) flux through channels in membrane of single smooth muscle cell (K^+ = potassium, α = alpha, β = beta, HI = histamine, SER = serotonin). (Reduced from magnification ×40,000.)

search in this area. It is becoming clear through these intensive investigations that the normal human epicardial coronary artery is not just a passive conduit through which blood flows but is a highly reactive structure in constant motion. These vessels are subject to and under the influence of a variety of mediators, including circulating vasoactive agents and local neurogenic mechanisms. Coronary artery spasm is an exaggerated or hypercontractile response of the vessel to these various factors.

The pathophysiologic mechanisms involved in coronary spasm most likely occur at the local cellular level. Many theories have been proposed and the highlights of each will be briefly reviewed.

Neurogenic Mechanisms

Neurogenic influences, especially from sympathetic stimulation, have been implicated in spasm. It is known that α-receptor stimulation mediates vascular smooth muscle contraction and that β_2-stimulation mediates relaxation. Ricci and coworkers[5] have postulated that alterations in sympathetic activity may result in spasm. They showed that α-adrenergic blockade with intravenously administered phentolamine hydrochloride immediately reversed coronary spasm. However, both α-blockers phentolamine and phenoxybenzamine hydrochloride are also direct smooth muscle relaxants by virtue of their calcium-blocking properties; thus it is unclear through what mechanisms these blockers are operating in patients with coronary spasm.

Robertson and colleagues[6] also studied sympathetic function in their patients with coronary spasm. They found normal catecholamine and metabolite levels in these patients. At the onset and termination of spontaneous ST segment elevation they found no change in catecholamine levels. The authors concluded that there was no generalized increase in sympathetic outflow associated with initiation of attacks of coronary spasm.

The ultimate evidence for neurogenic mechanisms not being implicated in the genesis of spasm is the use of surgical denervation procedures. Bertrand and associates[7] and Clark and co-workers[8] attempted complete denervation by surgical autotransplantation of the heart. Both groups were unsuccessful in completely eliminating spasm using this method. Buda and colleagues[9] recently reported a cardiac transplant patient in whom coronary spasm developed. Electrophysiologic studies showed complete denervation, but spasm was still evident.

These studies therefore show that denervation by itself does not prevent spasm. It appears that derangement of sympathetic nervous system function is not the cause of spasm. The sympathetic system may modulate or be secondarily involved, but it is not the sole mechanism causing abnormal contraction of coronary vascular smooth muscle.

Prostaglandins

The role of prostaglandins (PGs) in causing altered vascular reactivity has undergone extensive investigation. More specifically, attention has been directed to the role of thromboxane (Tx) A_2 as a vasoconstrictor and prostacyclin (PGI_2) as a vasodilator. TxA_2 is released by aggregating platelets and can cause intense vasoconstriction. PGI_2 is produced within the vessel wall and inhibits platelet aggregation. In low concentrations PGI_2 causes relaxation of smooth muscle and in high concentrations it causes contraction of smooth muscle.

Robertson and associates[10] studied the production of TxB_2 (the hydration product of TxA_2) in patients with spasm. They conclude that TxB_2 was unlikely to cause coronary spasm, though it may be released secondarily. They, as well as A. Maseri, MD (written communication, October 1980) have also studied the effects of cyclooxygenase inhibitors, such as indomethacin and aspirin, on coronary spasm, and they have found no effect of these agents on the frequency or duration of ischemic events due to spasm. All of these studies suggest that although PGs and platelets may be involved secondarily in spasm, they are not primary medicators.

Circulating Vasoactive Amines—Local Factors

Coronary artery spasm can be provoked clinically by a wide spectrum of agents. These include ergonovine,[11] methacholine,[12] norepinephrine,[13] TRIS buffer (tromethamine)[14] and histamine.[15] Each of these agents acts pharmacologically through specific receptors found in the cell membrane of individual smooth muscle cells. This implies that the pathophysiology of coronary spasm involves a cellular mechanism beyond the level of interaction of a single agonist and its membrane receptor and that this pathway can be activated by a number of endogenous vasoactive substances. Alternatively, it is possible that areas of spasm are marked by alterations of all classes of mem-

brane receptors and that spasm may result from activation of any of them. It is hoped that future research will define the precise mechanisms, but the evidence to date suggests that coronary artery spasm is due to local abnormalities at the single cell level.

Clinical Presentation

Definition

JOHN S. SCHROEDER, MD:* Coronary artery spasm is best defined as transient, reversible focal spasm in an epicardial coronary artery resulting in myocardial ischemia, which is reversible with nitroglycerin. It is now appreciated that not only normal but severely atherosclerotic arteries are dynamic vessels that are capable of responding to a number of autonomic and humoral influences that may precipitate the transient, recurrent focal spasm leading to rest or apparent unprovoked angina pectoris.

Classical Variant Angina

Patients with typical variant angina report episodes of angina that occur predominantly at rest or while asleep. The location and distribution of the angina pectoris is typical for myocardial ischemia and is usually described as a constricting or tight, oppressive sensation in the substernal area that may radiate into the neck, jaw or inner aspect of the left arm. The pain may occur without any evident provocation or, in some patients, may also appear during emotional excitement or after cessation of exercise. The more typical presentation is pain occurring cyclically in the early morning or that awakens the patient from sleep. Pain is typically responsive to nitroglycerin taken sublingually, which results in relief in a few minutes. Pain tends to be transient in nature and may be accompanied by feelings of anxiety or shortness of breath when severe myocardial ischemia causes left ventricular dysfunction and a rise in pulmonary venous pressures. A patient tends to have a similar pain pattern on a daily basis, though the frequency of pain can be highly variable, occurring frequently for a few days and then disappearing for a few days to several months.[16] This cyclic occurrence is important when considering provocative testing because when patients are in an active phase small amounts of ergonovine maleate may produce intense spasm.

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In patients with spasm there may be a history of migraine headaches, and almost all of these patients are heavy smokers. In addition, there may be an increased incidence of thyroid disease. Patients with variant angina may be diagnosed as neurotics or as having an anxiety reaction because of the transient nature of the symptoms and the fact that the angina occurs in a lower risk group for coronary artery disease. The diagnosis is established by recording ST segment shifts on electrocardiogram (ECG) during episodes of chest pain or by showing reversible spasm during coronary arteriography.

Unstable Angina Pectoris

Studies at Stanford[17,18] and by Maseri and coworkers[19] have clearly shown that patients with rest or nocturnal pain due to severe occlusive coronary disease have episodes of angina pectoris unrelated to increases in myocardial work or oxygen demand. Berndt and associates[18] from Stanford reported that, in patients admitted to the coronary care unit with unstable angina pectoris, there was little rise in the double or triple product (heart rate × blood pressure or heart rate × blood pressure × ejection time) at the very earliest onset of resting chest pain compared with resting values. This implies angina in the presence of no increase in myocardial oxygen demands. Furthermore, the little or no change in the double product was in marked contrast to the double product at the onset of pacing-induced angina, where there was approximately a 50 percent rise in double product before these same patients experienced angina associated with typical ST segment depression. These observations have been further documented by Maseri and colleagues[19] by repeat coronary arteriography in patients with unstable angina pectoris in whom transient occlusion in areas of previous occlusive disease have been reported during pain episodes. These clinical studies documenting vasoreactivity and superimposed focal spasm in areas of occlusive coronary disease have established the important role of coronary spasm in unstable angina pectoris or in patients with rest or nocturnal angina. The anginal pain of unstable angina pectoris tends to be characteristic of myocardial ischemia, with typical pain location and radiation pattern. However, the anginal pain may be less responsive to a single nitroglycerin tablet taken sublingually and require more intensive nitrate or calcium-blocker therapy. It is important in these patients as well

to record transient episodes of ST segment depression or elevation as objective proof of myocardial ischemia causing the rest or nocturnal pain.

It is now believed that transient complete coronary obstruction associated with ST segment elevation may be much more common than previously suspected in patients with unstable angina pectoris. For example, most of the patients in the National Heart, Lung, and Blood Institute trial for unstable angina had rest angina.[20] Furthermore, 25 percent had ST segment elevation during one or more chest pain episodes.[21] It is now appreciated that continuous ECG monitoring and, if at all possible, 12-lead electrocardiograms during chest pain are essential to document the ST segment shifts and to assist in locating the area of myocardial ischemia. Thus, the primary difference of these patients from those with classic variant angina is that they have moderate to severe underlying occlusive coronary disease and frequently have effort angina as well. Unless a patient is hypertensive or is having paroxysmal tachycardias as the cause of rest pain, we now believe that superimposed spasm may play a causal role in the unstable or preinfarction state.

Effort Angina

Coronary artery spasm may play a role in patients with typical effort angina, even when there is no rest or nocturnal component. Yasue and colleagues[22] have described the occurrence of spasm in patients with effort-induced angina when ST segment depression was present. This existence of "inappropriate" coronary artery spasm during effort angina remains primarily a theoretic concept, however, because reversal or prevention of spasm with nitrates or calcium antagonists does not permit a higher maximal myocardial oxygen demand or workload at the end of exercise. Variability in episodes of angina on a day-to-day basis and the presence of "walk-through angina" may be partially explained on the basis of inappropriate coronary artery spasm. It is likely, however, that coronary artery spasm plays a minimal role in patients with typical predictable angina of effort.

Diagnostic Methods

Once the diagnosis of coronary artery spasm is suspected in a patient with typical or atypical chest pain, it is helpful for the clinician to ask a series of questions regarding the proper approach to diagnosis in the patient.

- Is the chest pain characteristic of myocardial ischemia? Generally the presenting chest discomfort or anginal syndrome should be typical for angina pectoris in its substernal location, with radiation into the jaw or down the inner aspect of either arm. It may be associated with shortness of breath, palpitations, dizziness or even syncope. The pain should also be relieved by nitroglycerin if coronary spasm is playing an important causal role. Differential diagnosis in patients with rest pain includes a variety of gastrointestinal and chest wall pain syndromes.

- Have ECG changes been recorded with an episode of chest pain? Although it is likely that subtotal or minimal degrees of focal spasm may occur without chest pain or symptoms, it is important to record ST segment shifts on the electrocardiogram to be sure that the asymptomatic episodes are related to myocardial ischemia. For a clear-cut diagnosis, we require transient ST segment depression or elevation of over 0.1 mV for 0.08 seconds if at all possible. As will be discussed, a full 12-lead electrocardiogram can be extremely helpful in documenting ST segment shifts and determining the location of the myocardial ischemia. After administration of nitroglycerin it is useful to report whether these ST segment shifts return to baseline.

- Is the coronary spasm superimposed on severe occlusive coronary artery disease? The diagnosis of severe occlusive coronary artery disease should be suspected in a patient who has rest or nocturnal angina, with a history of effort-induced angina. This is particularly true in a patient with a high prevalence of coronary artery disease risk factors. In patients with this background, it is important not only to treat pain episodes, but to document the severity and extent of occlusive coronary disease.

- Could any of the patient's symptoms be due to arrhythmias? Coronary spasm is well known to produce a wide variety of atrial and ventricular arrhythmias. For example, spasm of the right coronary artery may cause episodes of complete heart block due to ischemia of the atrioventricular (AV) node. These patients may have transient chest pain followed by syncope or transient dizziness. In other patients, ventricular tachycardia or frequent premature ventricular contractions related to myocardial ischemia have been reported and

may precipitate symptoms of palpitations, dizziness or syncope as well. It is essential to relate a patient's chest pain or spasm to these arrhythmias because they are poorly responsive to traditional antiarrhythmic therapy and require prophylaxis or treatment of focal spasm.

Outpatient Approach to Diagnosis

DR. GINSBURG: Because it is essential to record ST segment shifts during episodes of chest pain that may be transient and unpredictable in nature, diagnosis in hospital or on an outpatient basis can be difficult to achieve. It is helpful to attempt initially to record ST segment shifts in patients suspected of coronary spasm on an outpatient basis in an effort to characterize both the frequency and location of the suspected myocardial ischemia (Table 1).[23]

Ambulatory ECG Monitoring

ECG monitoring for 24 to 48 hours may provide important diagnostic clues to a patient's problem by showing not only ST segment shifts, but also arrhythmias during symptomatic or asymptomatic periods of myocardial ischemia. This approach allows for the long-term continuous ECG monitoring that can be important in the outpatient diagnosis when a patient is having at least one episode of pain a day. In addition, the event marker on the ambulatory monitor and a patient diary permit correlation between symptoms and ST segment changes on the electrocardiogram. We use a two-channel recorder that has a sufficiently low frequency response (0.05 Hz) to detect 0.1 mV changes and ST segment shifts (Instruments for Cardiac Research, Inc., New York, ICR Model 7201 and Scanner ICR Model 6201G-2b). It is important to record both channels of the ECG, an inferior and an anterior lead, to be able to see all possible changes of an ST segment shift during pain. This information can be very helpful also in subsequent inpatient studies if the suspected coronary artery involved in spasm can be identified. In addition, we have observed a number of patients with right coronary artery spasm who have transient episodes of second-degree or complete heart block associated with periods of dizziness or syncope without chest pain (Figure 2).

The scanning technician must be made aware that transient ST segment shifts are one of the primary reasons for an ambulatory Holter recording. All symptomatic episodes should have careful analysis of simultaneous periods of ECG recording for either ST depression, ST elevation or return to normal of T wave inversion. Figure 2 shows an example of transient heart block due to right coronary artery spasm that was unassociated with chest pain and led to the correct diagnosis of spasm.

Self-Initiated Transtelephonic ECG Monitoring

In a patient with infrequent and unpredictable episodes of chest pain, it may be difficult to record

TABLE 1.—*Noninvasive and Invasive Evaluation of Coronary Artery Status*

- Noninvasive
  - Detailed history and physical
  - Electrocardiographic monitoring
    - Two-channel continuous ambulatory monitor with chest pain diary
    - In-hospital 12-lead ECG during and after pain
    - In-hospital continuous telemetry
    - Self-initiated transtelephonic monitoring during pain
- Invasive
  - Coronary arteriography (off all medications) with ergonovine provocation

ECG = electrocardiogram

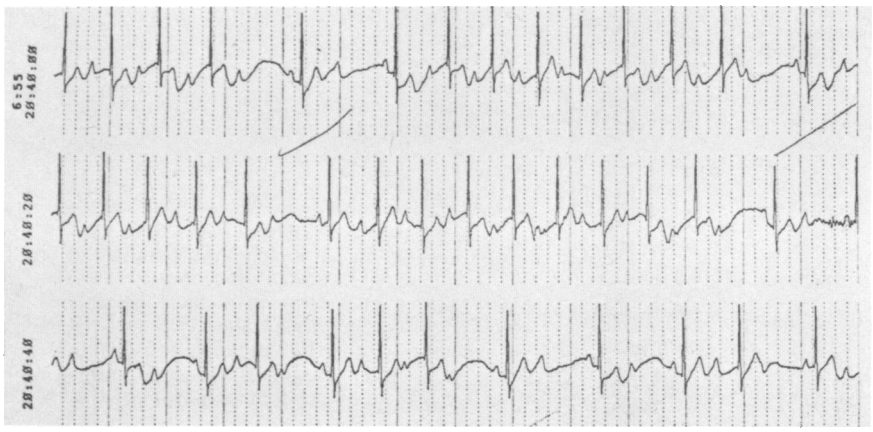

Figure 2.—Computer printout of Holter electrocardiogram recording showing transient second degree heart block.

ST segment shifts by 24- or 48-hour ambulatory ECG monitoring. For these patients we have been using the Cardiobeeper (Survival Technology, Bethesda, MD), which is a bipolar-lead system with a low frequency response for transmission of electrocardiograms.[24] Patients are instructed to keep the ECG electrodes attached to their chest at all times. When an episode of chest pain occurs, they can quickly attach the leads to the previously attached electrodes and, by any available telephone, transmit an electrocardiogram during a pain episode. The single-lead electrocardiogram is then tape recorded for later conversion to a rhythm strip for review and analysis. Figure 3 shows a typical episode of ST segment elevation that was transmitted and compared with a previously transmitted baseline electrocardiogram during a pain-free period. The primary advantage of this system is its use in patients with cyclic or infrequent episodes of pain and the fact that it can be used relatively inexpensively over long periods of time. The primary disadvantage is that it is a single-channel recorder and may miss ST segment changes in other leads and will miss arrhythmias or ST segment shift when a patient is not symptomatic.

Treadmill Exercise Testing

When evaluating a case of suspected focal coronary artery spasm, it is helpful to ascertain whether a patient may have underlying occlusive coronary disease as well. For this reason a treadmill exercise test, during which time repeated 12-lead electrocardiograms can be recorded, is very helpful in an outpatient evaluation. Patients with typical variant angina pectoris and normal coronaries generally have excellent exercise tolerance with no ST segment shifts or pain during maximal exercise. A small percentage of these patients may have postexercise chest pain and ST segment elevation or depression, possibly due to autonomic disturbance during recovery from exercise. In a patient in whom typical effort angina develops with ST segment depression, the clinical impression of occlusive artery disease, possibly with superimposed spasm, can be established. Outpatient testing using ECG monitoring and treadmill exercise test does not necessarily supplant the need for inpatient evaluation and coronary arteriography but will provide a basis for the suspected role of spasm in a patient and assist in locating the responsible coronary artery. Furthermore, the recording of arrhythmias during symptomatic or asymptomatic periods of spasm may help explain previously unexplained symptoms before hospital admission.

In-hospital Diagnostic Approach

Because rest or nocturnal angina may be a symptom of severe occlusive coronary artery disease or preinfarction angina, it is important to proceed with hospital evaluation and coronary arteriography, if this has not been previously accomplished. It is extremely helpful to be able to observe patients in hospital during an episode of chest pain, at which time a 12-lead electrocar-

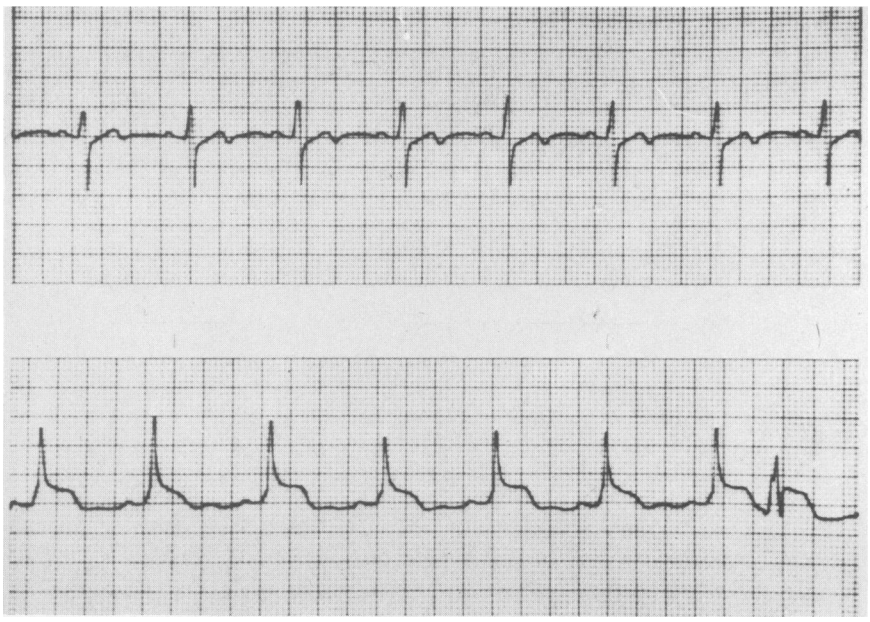

Figure 3.—Rhythm strip from transtelephonic transmission of electrocardiogram. The top strip is a baseline recording while patient is free of pain. The bottom strip shows ST segment elevation during episode of chest pain.

diogram can be obtained before they take nitroglycerin. Orders must be clearly written requesting a stat electrocardiogram during chest pain and not allow any symptomatic treatment of the chest pain before recording the ST segment shift. Figure 4 shows a 12-lead electrocardiogram during moderately severe episodes of chest pain and return to baseline three hours later. A patient with nocturnal episodes of chest pain can be attached at bedtime to a three-lead automatic ECG machine and instructed to push the automatic start button to record the electrocardiogram when awakened by chest pain. This approach does not depend on other medical personnel while the patient is having acute chest pain and it facilitates the recording of ST segment shift and allows earlier taking of medication for relief of symptoms.

Ergonovine Provocation During Coronary Arteriography

DR. SCHROEDER: A carefully planned coronary arteriogram in a patient with suspected coronary spasm nearly always provides conclusive answers. It allows determination of the extent of fixed atherosclerotic occlusive coronary disease and whether focal spasm may be playing a role. Before coronary arteriography, patients are tapered off all long-acting nitrates, nitroglycerin ointment formulations, beta blockers and calcium antagonists. Patients are permitted to take nitrate sublingually for episodes of chest pain as needed, but if at all possible no other cardiovascular medications are used. Premedication should be minimal and no antihistamines given. It is essential to obtain consent not only for coronary arteriography but for ergonovine administration before arteriography is done.

First routine coronary arteriography is done. If the coronary arteries are normal or have insufficient fixed occlusive disease to explain a patient's rest angina symptoms, ergonovine maleate testing is then undertaken.[11,25] Radiolucent electrode pads are placed on the chest wall for a complete 12-lead electrocardiogram and a 3-channel, 12-lead ECG machine is attached. The protocol for ergonovine challenge is outlined in

Figure 4.—Twelve-lead electrocardiogram strip taken during chest pain showing pronounced ST segment elevation in the anterolateral leads **(top)** and three hours after resolution of the pain **(bottom).**

Table 2. A solution of nitroglycerin must be made up before initiation of the provocative testing to allow expeditious treatment of any induced spasm (Table 3). If there is a history of possible heart block associated with the pain as indicated by symptoms or by previous ECG monitoring, a right ventricular pacing wire should also be positioned. If the Judkin's technique for coronary arteriography is being used, the catheter for the artery most suspected of spasm should remain in position during the ergonovine testing.

The ergonovine is given by intravenous bolus in three doses: 0.05 mg, 0.1 mg and 0.25 mg. It is absolutely essential to allow at least three minutes after each bolus injection during which time an ECG is taken at 1½ and 3 minutes. If chest pain develops or there are ECG changes compatible with ischemia, a coronary artery injection is made. It may be necessary to exchange catheters quickly with the Judkin's technique if the first one does not show spasm but there are clear-cut ST segment shifts in another area on the electrocardiogram. If pain or ST segment shifts do not occur after the final dose, each coronary artery must be reinjected because occasionally subtotal focal occlusion may occur without major symptoms or ST segment shifts. If there are no symptoms or ECG changes and at least five minutes have gone by since the last injection of ergonovine, nitroglycerin should be given and the study completed.

If focal spasm is recorded, it is essential not to repeat injections of contrast material into various angles of the occluded artery. The spasm can be reversed with intravenous administration of nitroglycerin. In difficult cases nitroglycerin can be administered intracoronary in an initial dose of 0.05 to 0.1 mg and repeated one to three times with the patient monitored for hypotension.

TABLE 2.—*Protocol for Ergonovine Challenge*

Obtain informed consent

No premedication

Prepare ergonovine and nitroglycerin for intravenous administration

Crash cart available

Minimum Interval Time (minutes)	*Dose of Ergonovine (mg)*	*Obtain Electrocardiogram*
0.0		✓
	0.05 (1 ml)	
1.5		✓
3.0		✓
	0.1 (2 ml)	
4.5		✓
6.0		✓
	0.25 (5 ml)	
7.5		✓
9.0		✓

Stop test as soon as chest pain or ST segment shift occurs

Reverse spasm with sublingual, intravenous or intracoronary administration of nitroglycerin as soon as documented

TABLE 3.—*Preparing Drugs for Ergonovine Provocation Test*

Prepare ergonovine

- Fill 10 ml syringe with 0.4 mg (2 ml) ergonovine maleate (Ergotrate, Eli Lilly and Co.) and 6 ml sterile water
- Final concentration: 0.05 mg per ml

Prepare nitroglycerin for intravenous administration

- Drop two 0.4 mg nitroglycerin tablets inside 10 ml syringe
- Fill syringe with 8 ml sterile water, replace barrel of syringe and shake
- Place Millipore filter (Milex®-GI, Millipore Corp., Bedford, MA) on end of syringe
- Final concentration: 100 μg per ml (must be prepared fresh each time)

Interpretation of Results

Cipriano and colleagues[25] have shown that there is a normal dose-related response of coronary arteries to ergonovine provocation. Generally, diffuse narrowing of less than 20 percent occurs (Figure 5). In patients with normal or essentially normal coronary arteries, diffuse or focal spasm with over 70 percent occlusion of the lumen is consistent with coronary artery spasm (Figure 6). However, unless there are accompanying symptoms of chest pain typical of a patient's pain pattern or ECG changes consistent with myocardial ischemia —whether it be ST depression or ST elevation— the diagnosis is not firmly established. We believe that it is safe to administer ergonovine in patients with occlusive coronary disease as long as the severity of the lesions does not explain their rest pain, that is, generally less than 50 percent occlusion. In these patients, focal spasm is usually observed in an area of atherosclerotic disease and should also cause an observed 70 percent or more reduction in luminal size. Focal spasm is confirmed by associated chest pain and evidence of myocardial ischemia on the electrocardiogram. The administration of ergonovine to patients with severe fixed obstructive disease is dangerous and may provoke myocardial infarction. Once recorded, spasm should be reversed as soon as possible as previously discussed.

Studies with ergonovine provocation at Stanford

University Medical Center and the University of Florida have documented the safety and reproducibility of this test.[11,26,27] In patients with typical variant angina without fixed obstruction, it appears to be specific and sensitive. In patients who are not suspected of having coronary spasm or who have atypical chest pain related to mitral valve prolapse, chest pain may be observed in 10 percent to 20 percent of cases but without associated ST segment shifts or focal spasm seen on arteriography. The risk of this procedure is in inducing spasm with associated myocardial ischemia and potential arrhythmias. A small number of deaths have been reported and in most cases were due to the injudicious use of large initial doses of ergonovine, not waiting an adequate time between doses or not documenting focal spasm because of lack of symptoms, or not being prepared to reverse spasm with intravenous or intracoronary administration of nitroglycerin.[28]

Outpatient testing with ergonovine in the same cautious, systematic manner can be done in patients who have had previously documented normal coronary arteries and who do not have symptoms of syncope or dizziness that might reflect heart block or ventricular tachycardia. In these patients an intravenous line should be started and blood pressures taken regularly. Ergonovine and nitroglycerin are prepared as previously described.

We consider the ergonovine study to be positive if there are electrocardiographic changes of ST segment elevation or depression of 0.1 mm or more associated with chest pain that is similar to a patient's usual pain pattern. As soon as a patient has chest pain and associated ST segment shifts, nitroglycerin is administered intravenously

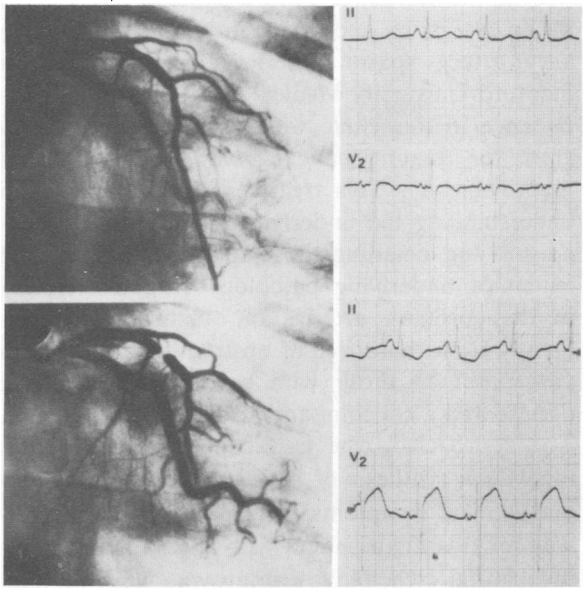

Figure 6.—Photographs and rhythm strips of left coronary arteriogram showing normal vessels in top panel and pronounced focal spasm of the left anterior descending artery with associated ST segment elevation in lead V_2 in the lower panel.

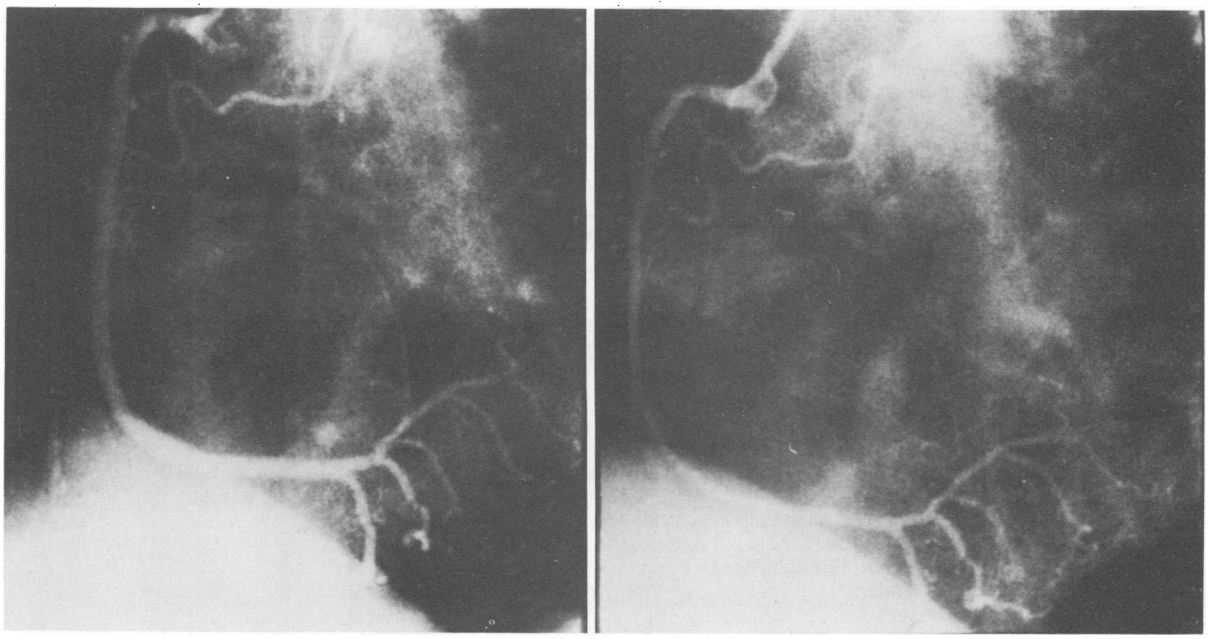

Figure 5.—Photographs of coronary arteriogram of the right coronary artery during control **(left)** and after administration of 0.25 mg of ergonovine maleate showing the diffuse 20 percent narrowing of the artery **(right)**.

(50 to 100 μg). The patient should be carefully monitored for hypotension or continued ischemia and given additional nitroglycerin intravenously as necessary. A patient is monitored and observed until the ECG findings return to normal.

Treatment of Coronary Artery Spasm

DR. GINSBURG: Since 1979 a clinic devoted solely to the evaluation and treatment of suspected coronary artery spasm has been in operation at Stanford University Medical Center. From our experience in this clinic we have developed a program for treating patients with coronary spasm (see Table 4). This treatment is based on both understanding the underlying pathogenetic mechanisms and detailing the clinical symptoms. The extent of underlying pathology (atherosclerosis) in the coronary arteries of our patients varies greatly from those free of obstructive disease with vasospasm to those with severe atherosclerotic disease and a concomitant vasospastic component. The approach to the treatment of these patients involves a synthesis of both underlying pathology and clinical symptoms. The final common pathway for treating a patient with angina is to reduce myocardial ischemia by improving flow of oxygenated blood, decreasing demand for it or some combination of the two.

The specific treatment of coronary artery spasm includes the following:

Nitrates

Nitroglycerin is the most effective agent available for aborting acute bouts of spasm and for prophylaxis. The method of administration of nitrates depends on the clinical situation. Prophylactic treatment for spasm incorporates the use of long-acting nitrates such as isosorbide dinitrate (20 to 240 mg a day), time-suspension capsules (5 to 10 mg a day) or nitroglycerin paste (1 to 12 inches a day). Sublingual nitroglycerin (0.3 to 0.6 mg) can be used effectively by patients to abort episodes of chest pain.

In patients who have coronary artery spasm provoked by pharmacologic agents such as ergonovine, intravenously administered nitroglycerin (50 to 150 μg bolus) should be given. In the catheterization laboratory nitrates can be administered either intravenously or into the coronary artery (100 to 300 μg). It should be remembered that spasm can occasionally be refractory to nitroglycerin and up to 1 mg a minute may sometimes have to be administered intravenously.

Calcium Entry Blockers

Calcium blockers, including diltiazem hydrochloride, nifedipine and verapamil, are the agents

TABLE 4.—*Treatment of Coronary Artery Spasm*

	Drugs
On Basis of Mechanisms	
Coronary spasm without significant obstructive coronary artery disease	Nitrates and/or calcium blockers
Coronary spasm with significant obstructive disease	1. Ca blockers alone or 2. Ca^+ blockers + beta blockers or 3. Ca^+ blockers + coronary bypass surgery

Drug	*Dose*	*Major Side-Effects*
Pharmacologic Agents		
Administration of nitrates		
Sublingual	0.3-0.6 mg	Hypotension; headache
Paste	1-12 in/day	Hypotension; headache
Oral	20-120 mg/day	Hypotension; headache
Intravenous	50-150 μg bolus	Hypotension; headache
Intracoronary	100-300 μg bolus	Hypotension; headache
Calcium blockers		
Diltiazem* (Cardizem)	240-360 mg/day	None
Nifedipine† (Procardia)	30-180 mg/day	Hypotension; pedal edema
Verapamil‡ (Isoptin)	80-480 mg/day	Constipation
Phentolamine hydrochloride (Regitine)		Not useful
Phenoxybenzamine hydrochloride (Dibenzyline)		Not useful
Propranolol hydrochloride (Inderal)		Not useful
Metoprolol tartrate (Lopressor)		Not useful

*Not available in the United States.
†Available in the United States as an oral preparation only.
‡Available in the United States as an intravenous solution only.

of choice in treating coronary spasm. Orally given nifedipine and intravenously given verapamil are now available. Diltiazem and an oral preparation of verapamil should be released soon by the Food and Drug Administration.

Although these three drugs are grouped under the general heading of calcium entry blockers, each drug has its own specific pharmacologic and pharmacokinetic mechanisms of action and adverse reactions. Each drug has specific clinical indications and relative contraindications. Understanding their pharmacologic activity is essential for administration. Each agent's effectiveness is also dependent on the underlying pathophysiology of the patient's clinical symptoms.

Diltiazem.[29] This agent's primary action is on the coronary artery bed, so it is effective in the treatment of spasm. The usual dosage is 240 to 360 mg a day given in divided doses every six hours. Adverse reactions have been almost nonexistent at these dosages. Diltiazem can be given safely with beta blockers or nitrates. Relative contraindications include AV conduction disease or severe left ventricular failure.

Nifedipine.[30] This agent has also proved effective in treating coronary spasm. Nifedipine is given in dosages of from 30 to 180 mg a day. It has no effect on the conduction system but does dilate the peripheral arterial bed and the coronary arteries. Thus the drug is also useful in severe hypertension or in reducing peripheral vascular resistance. Side effects include orthostatic hypotension, reflex tachycardia and pedal edema. Nifedipine can be given safely with beta blockers and nitrates and to patients with congestive heart failure.

Verapamil.[31] Verapamil is a very effective agent in the treatment of coronary spasm, as well as in the treatment of supraventricular arrhythmias. Dosages are from 80 to 480 mg a day, given on an every-six-hour dose schedule. Verapamil should not be used in patients with conduction disease or congestive heart failure. Side effects include nausea, vomiting and constipation. Verapamil can be given along with nitrates and beta blockers if there is no conduction disease or failure.

Membrane Receptor Blockade

The pathologic mechanism of coronary spasm is most likely due to an abnormality beyond the level of a single membrane receptor. Therefore, specific receptor blockage with α-, β-, muscarinic or histaminic antagonists would not be expected to be effective. Experience with phentolamine or phenoxybenzamine hydrochloride has shown that these agents are only occasionally effective and and not without significant side effects. They probably operate by their nonspecific vasodilating properties. Beta blockers are also not useful in the treatment of coronary spasm as they have no vasodilator action. However, this should be clarified with respect to patients who have spasm superimposed on hemodynamically significant stenosis. In these patients a combination of calcium blockers (to treat spasm) and beta blockers (to decrease myocardial demand) is very useful and effective therapy.

Surgical Denervation

Complete or partial denervation of the human heart is an interesting procedure historically in the treatment of spasm but has no place in the present treatment of spasm.

Risk Factor Reduction

Coronary spasm nearly always occurs in areas of atherosclerosis, regardless of the degree. Therefore, aggressive attempts should be made to decrease risk factors. This is especially true of cigarette smoking, since our experience has been that 85 percent to 90 percent of patients with spasm are cigarette smokers. Blood pressure should be kept under control and weight reduction and lowering of cholesterol attempted.

Pacemakers

Arrhythmias are quite common in patients during periods of active spasm. These arrhythmias, such as AV block, sinus bradycardia and ventricular tachycardia or fibrillation, are secondary events due to ischemia. Treatment of these arrhythmias consists of prevention because if coronary spasm is prevented by aggressive treatment, then arrhythmias are not a problem. Pacemaker insertion is not indicated for bradycardia or AV block due to spasm unless these phenomena are the result of processes unrelated to spasm.

REFERENCES

1. Prinzmetal M, Kemnamer R, Merliss R, et al: Angina pectoris—1. The variant forms of angina pectoris. Am J Med 1959; 27:375

2. Osler W: The Lumleian Lectures on angina pectoris. Lancet 1910; 1:699

3. Wilson F, Johnston F: The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction. Am Heart J 1941; 22:64

4. Ginsburg R, Bristow MR, Harrison DC, et al: Studies with isolated human coronary arteries. Chest 1980 Jul; 78(Suppl):180-186

5. Ricci DR, Orlick AE, Cipriano PR, et al: Altered adrenergic activity in coronary arterial spasm: Insight into mechanism based on study of coronary hemodynamics and the electrocardiogram. Am J Cardiol 1979 Jun; 43:1073-1079

6. Robertson D, Robertson RM, Nies A, et al: Variant angina pectoris: Investigation of indexes of sympathetic nervous system function. Am J Cardiol 1979 Jun; 43:1080-1085,

7. Bertrand ME, Lablanche JM, Talment PY, et al: Complete denervation of the heart (autotransplantation) for treatment of severe refractory coronary spasm. Am J Cardiol 1981; 47:1376-1378

8. Clark DA, Quint RA, Mitchell RL, et al: Coronary artery spasm: Medical management, surgical denervation, and autotransplantation. J Thorac Cardiovasc Surg 1977 Mar; 73:332-339

9. Buda AJ, Fowles RE, Schroeder JS, et al: Coronary artery spasm in the denervated transplanted human heart. Am J Med 1981; 70:1144-1148

10. Robertson RM, Robertson D, Roberts LJ, et al: Thromboxane in vasotonic angina pectoris with evidence from direct measurements and inhibitor trials. N Engl J Med 1980; 304: 998-1003

11. Schroeder JS, Bolen JL, Quint RA, et al: Provocation of coronary spasm with ergonovine maleate—New test with results in 57 patients undergoing coronary arteriography. Am J Cardiol 1977 Oct; 40:487-491

12. Endo M, Hirosawa K, Kaneko N: Prinzmetal's variant angina—Coronary arteriogram and left ventriculogram during angina attack induced by methacholine. N Engl J Med 1976 Jan 29; 294:252-255

13. Yasue H, Touyama M, Shimamoto M, et al: Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 1974 Sep; 50:534-539

14. Yasue H, Nagao M, Omote S, et al: Coronary arterial spasm and Prinzmetal's variant form of angina induced by hyperventilation and Tris-buffer infusion. Circulation 1978 Jul; 58:56-62

15. Ginsburg R, Bristow MR, Kantrowitz N, et al: Histamine provocation of clinical coronary artery spasm: Implications concerning pathogenesis of variant angina pectoris. Am Heart J 1981; 102:819-822

16. Allaire BI, Schroeder JS: Prinzmetal's angina—Clinical and anatomic aspects. West J Med 1975 Mar; 122(3):187-193

17. Cannom DS, Harrison DC, Schroeder JS: Hemodynamic observations in patients wtih unstable angina pectoris. Am J Cardiol 1974 Jan; 33:17-22

18. Berndt TB, Fitzgerald J, Harrison DC, et al: Hemodynamic changes at the onset of spontaneous versus pacing-induced angina. Am J Cardiol 1977 May 26; 39:784-788

19. Maseri A, L'Abbate A, Baroldi G, et al: Coronary vasospasm as a possible cause of myocardial infarction—A conclusion derived from the study of preinfarction angina. N Engl J Med 1978 Dec 7; 299:1271-1277

20. Russell RO, Karp R, Resnekov L, et al: Unstable angina pectoris: National cooperative study group to compare medical and surgical therapy—I. Report of protocol and patient population. Am J Cardiol 1976; 37:896-908

21. Schroeder J, Russell R, Resnekov L, et al: Unstable angina pectoris: National randomized study of surgical versus medical therapy—Results in Prinzmetal-type angina. Am J Cardiol 1978; 41:397-402

22. Yasue H, Omote S, Takizawa A, et al: Exertional angina pectoris caused by coronary arterial spasm—Effects of various drugs. Am J Cardiol 1979 Mar; 43:647-652

23. Ginsburg R, Schroeder JS: Coronary artery spasm: Approach to diagnosis and treatment. Practical Cardiology 1980; 24-34

24. Ginsburg R, Lamb I, Schroeder JS, et al: Long-term transtelephonic electrocardiographic monitoring in the detection and evaluation of variant angina. Am Heart J 1981; 102:196-201

25. Cipriano PR, Gunthaner DF, Orlick AE, et al: The effects of ergonovine maleate on coronary arterial size. Circulation 1979; 59:82-89

26. Curry RC Jr, Pepine CJ, Sabom MB, et al: Effects of ergonovine in patients with and without coronary artery disease. Circulation 1977 Nov; 56(5):803-809

27. Curry RC Jr, Pepine CJ, Sabom MB, et al: Similarities of ergonovine-induced and spontaneous attacks of variant angina. Circulation 1979 Feb; 59(2):307-312

28. Buxton A, Goldberg S, Hirschfeld JW, et al: Refractory ergonovine-induced coronary vasospasm: Importance of intracoronary nitroglycerin. Am J Cardiol 1980 Aug; 46(2):329-334

29. Rosenthal SJ, Ginsburg R, Lamb I, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. Am J Cardiol 1980; 46:1027

30. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-spasm—Experience in 127 patients. N Engl J Med 1980 Jun 5; 302:1269-1273

31. Johnson SM, Mauritson DR, Hillis LD, et al: Verapamil in the treatment of Prinzmental's variant angina: A long-term, double-blind, randomized trial, abstracted. Am J Cardiol 1981; 47:399